Clinical impact of virological failure and resistance analysis definitions used in pivotal clinical trials of initial antiretroviral treatment: a systematic review.

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Methods.

Systematic review of all phase III RCTs1–5 including preferred once-daily ART (European AIDS guidelines)13 or recently approved by the FDA, according PRISMA guidelines.20

Results.

-16 Treatment arms (14 RCTs) with 6,175 participants treated with delategravir (DTG), bictegravir (BIC), elvitegravir/cobicistat (EVC/g), raltegravir (RAL), darunavir/cobicistat (DRV/c), rilpivirine (RPV) or doravirine (DOR) (Table 1). -Plasma HIV-1 RNA thresholds for PDVF or RAP ranged from 40 to 50, 200, 400 and 500 copies/mL (Table 2). -Only eight treatment arms assessed all participants with PDVF. Most of the remaining eight arms genotyped roughly ≥50% of those with PDVF. Overall, 85/296 (29%) patients with PDVF were not genotyped. We found a strong evidence of a linear correlation between the higher HIV-1 RNA threshold for genotyping and increasing rates of patients with PDVF that were not eventually genotyped (Table 3). -No resistance was detected against the third drug or the backbone nucleos(t)ide reverse transcriptase inhibitors (NRTI) in any participants with DTG, BIC or DRV/G. EVC/G and RAL and RPV showed selection of HIV-1 resistance against both the third drug and the NRTIs in the backbone in approximately 50% of the participants with PDVF and genotypes sufficiently performed. -Percentages of participants with drug resistance mutations selected at VF, and participants meeting PDVF criteria but with no genotype data available (not genotyped for HIV failure or failed amplification) were shown, in Table 4 and Figure 1.

Conclusions.

1-The absence of standardised definitions of VF and criteria for resistance testing in pivotal phase III RCTs of first-line ART leads to the possibility of underreporting of resistance mutations when genotypes are only performed at higher viral load cut-offs.

2-Stringent homogeneous criteria should be defined to ensure that all participants with PDVF (confirmed HIV RNA ≥50 copies/mL and the second >200 copies/mL) undergo genotyping.

References.